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$Pd(OAc)_2$ Catalyzed Olefination of Highly Electron-Deficient Perfluoroarenes

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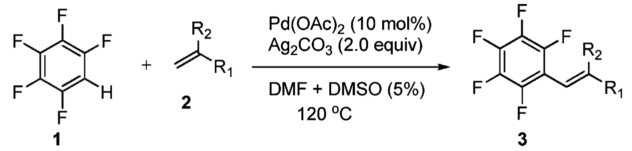
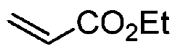
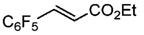
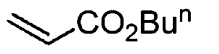
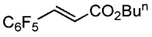
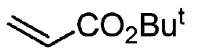
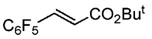
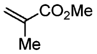
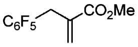
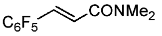
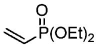
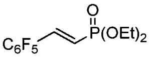
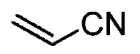
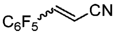
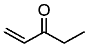
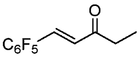
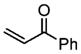
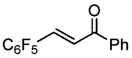
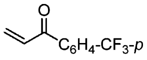
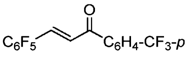
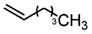
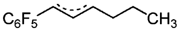
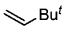
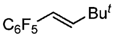
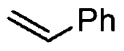
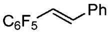
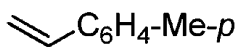
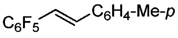
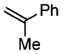
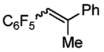
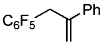
Perfluoroarenes constitute a distinct class of fluorinated compounds due to their importance in materials and life science.[1] Usually, they can be prepared from perfluoroaryl metals, halides, or aldehydes.[1d,2] However, this "prefunctionalization" process has intrinsic drawbacks in terms of atom and step economy. Recently, the direct arylation, alkenylation and alkylation of perfluoroarenes were reported by Fagnou,[3] Daugulis,[4] and Nakao and Hiyama,[5] respectively. While, these approaches are attractive, new methods for the direct alkenylation of perfluoroarenes remain highly desirable in view of the requirement of alkenyl halides as substrates[4] or employment of an air-sensitive Ni(0) catalyst that is only suitable for internal alkynes in this process[5] in these prior studies. However, unlike the direct olefination of electron-rich arenes,[6−8] reactions of electron-deficient arenes are still a great challenge, and only rare examples have been reported.[9] The reason is that the electron-deficient arenes are nonreactive due to their poor coordination with $Pd(OAc)_2$.[9a,d] In addition, the σ-bonds between transition metals and perfluorinated groups, such as the highly electron-deficient pentafluorophenyl group ($M-C_6F_5$), are particularly strong and reluctant to reaction.[2c,d,10] Pioneering work on insertion of alkenes into the $M-C_6F_5$ bond using catalytic $(NBu_4)_2[Pd_2(\mu\text{-}Br)_2(C_6F_5)_2Br_2]$ has been reported by Espinet and Milstein and co-workers.[2c,d] This work represents an impressive example of transition metal catalysis to access organofluorine compounds, but fluorinated arylhalides were required and nonactivated alkenes such as aliphatic and electron-rich alkenes were less promising substrates. Herein, we report a first example of $Pd(OAc)_2$ catalyzed direct olefination of highly electron-deficient perfluoroarenes with a broad range of substrates in moderate to high yields and with moderate to high stereo- and regioselectivities.

Initially, a highly electron-deficient pentafluorobenzene **1** and ethyl acrylate **2a** were chosen as model substrates for this study. After a survey of reaction conditions we found that the solvent, oxidants, and Pd catalysts are critical for the reaction efficiency (see Supporting Information). A mixed solvent system of 5% DMSO in DMF was found to be the optimum reaction medium. The reaction carried out with **1** (1 equiv), **2a** (2 equiv), and Ag_2CO_3 (2 equiv) which functions as both a base and oxidant in the presence of $Pd(OAc)_2$ (10 mol %) at 120 °C provided **3a** in good yield (78%, mixture of *E*/*Z* isomers, $E/Z = 14:1$). Other oxidants such as $Cu(OAc)_2$, oxone, BQ, $PhI(OAc)_2$, and O_2 or other Pd catalysts ($PdCl_2$, $Pd(TFA)_2$, and $Pd_2(dba)_3$) showed less or no activity.

A great variety of pentafluorophenyl substituted alkenes can be generated via this method (Table 1). The alkenylation of **1** worked well for electron-deficient olefins bearing ester, amide, phosphonate, or ketone groups, and moderate to excellent yields and high stereoselectivities were obtained (entries 1−6, 8−10). For some entries, removal of the minor *Z*-isomer required reversed-phase preparative HPLC. Interestingly, in the case of branched olefin **2d**, constitutional isomer **4d** was obtained as the major product (entry 4). Acrylonitrile **2g** was also tolerated, and a 34% yield of a mixture ($E/Z = 1.4:1$) of isomers of **3g** was provided (entry 7). Notably, the nonactivated aliphatic olefins **2k−l** underwent smooth reactions in good yields (entries 11−12), which is in sharp contrast to previous results.[2c,d] Moreover, electron-rich alkenes were readily reacted with **1** in good yields (entries 13−15). For **2o**, a mixture of constitutional isomers **3o** and **4o** were formed (entry 15).

Table 1. Oxidative Olefination of Pentafluorobenzene with Various Alkenes[a]



entry	alkene **2**	product **3**	yield (%)[b], (*E*/*Z*)[d]
1	 **2a**	 **3a**	69[c]; (14:1)
2	 **2b**	 **3b**	69[c]; (15:1)
3	 **2c**	 **3c**	64[c]; (13:1)
4[e]	 **2d**	 **4d**	68[c]
5	 **2e**	 **3e**	74, *E* only
6	 **2f**	 **3f**	83[c]; (12:1)
7[f]	 **2g**	 **3g**	34, (1.4:1)
8[f]	 **2h**	 **3h**	44, (60:1)
9	 **2i**	 **3i**	61, (50:1)
10	 **2j**	 **3j**	55, (23:1)
11	 **2k**	 **3k**	85[g]
12[e]	 **2l**	 **3l**	83, (50:1)
13	 **2m**	 **3m**	90, (50:1)
14	 **2n**	 **3n**	71, *E* only 80[e], *E* only
15	 **2o**	 **3o**  **4o**	65[g] **3o** (10:1) / **4o** = 1.3:1

[a] Reaction conditions unless otherwise specified: **1** (0.6 mmol), **2** (2.0−3.0 equiv), and DMF (2.4 mL) + DMSO (120 μL) for 10−12 h. [b] Isolated yield. [c] Yield after purification by reversed-phase preparative HPLC. [d] Determined by ^{19}F NMR. [e] Using 20 mol % $Pd(OAc)_2$, 3.0 equiv of Ag_2CO_3 for 12−24 h. [f] Using 20 mol % $Pd(OAc)_2$, 3.0 equiv of Ag_2CO_3, and 4.0 equiv of alkene. [g] Isolated yield of mixtures of constitutional isomers (see Supporting Information).

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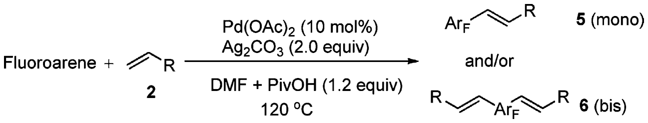
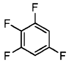
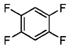
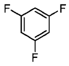
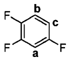
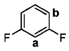
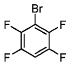
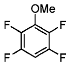
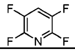
The substrate scope with respect to fluoroarenes was also tested, and representative results are summarized in Table 2.[11] We found that using 10 mol % of $Pd(OAc)_2$, 1.2 equiv of PivOH[12] instead of DMSO (5%), and 4.0 equiv of fluoroarenes afforded alkenylated products in moderate yields with moderate to good regioselectivities (for details see Supporting Information). Generally, the reaction with electron-rich alkene **2m** afforded higher yields than that of electron-deficient alkene **2c**. The most acidic C−H bonds located between two fluorines (entries 1−2, 4−5) are primary reaction sites and provided mostly monoalkenylated products in higher yields than substrates with C−H bonds ortho to only one fluorine, such as 1,2,3,4-tetrafluorobenzene (entry 3). However, in the monoalkenylation of 1,2-difluorobenzene to give **5fa** or **5fb**, a decreased regioselectivity between position **a** (**5faa** or **5fba**) and position **b** (**5fab** or **5fbb**) was observed (**5faa/5fab** = 2:1, **5fba/5fbb** = 2:1) (entry 6). It is worth noting that an arylbromide was also tolerated by the reaction conditions (entry 7) providing opportunities for further functionalization. Furthermore, substrates with an electron-donating methoxy group and fluorinated pyridine also furnished the alkenylated products in moderate to good yields (entries 8−9).

Table 2. Oxidative Olefination of Fluoroarenes with Alkenes[a]

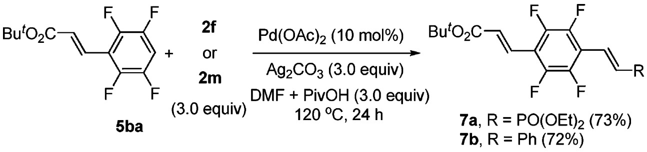


entry	fluoroarene	R	yield (%),[b] **5**	yield (%),[b] **6**
1		CO_2Bu^t Ph	62 (**5aa**) 73 (**5ab**)[c]	8 (**6aa**) 15 (**6ab**)[c]
2		CO_2Bu^t Ph	66 (**5ba**) 63 (**5bb**)	8 (**6ba**) 26 (**6bb**)
3		CO_2Bu^t Ph	44 (**5ca**) 48 (**5cb**)	--- ---
4		CO_2Bu^t Ph	63 (**5da**) 62 (**5db**)	18 (**6da**) 13 (**6db**)
5		CO_2Bu^t Ph	55 (**5ea**), (3:1)[d] 54(**5eb**),(3.6:1)[d]	--- trace
6		CO_2Bu^t Ph	61(**5fa**), (2:1)[d] 46 (**5fb**), (2:1)[d]	5 (**6fa**) ---
7[e]		CO_2Bu^t Ph	61 (13:1)[g], (**5ga**)[f] 61 (**5gb**)	12 (**6ga**) ---
8[e]		CO_2Bu^t Ph	38 (10:1)[g], (**5ha**) 60, (**5hb**)	--- ---
9[h]		CO_2Bu^t Ph	69 (**5ia**)[i] 72 (**5ib**)	--- ---

[a] Fluoroarene (4.0 equiv), **2** (0.6 mmol), DMF (2.4 mL) for 18−24 h. [b] Isolated yield. [c] 5% DMSO was used instead of PivOH. [d] Isolated yield of mixtures of regioisomers, number in parentheses is the regioselectivity between position **a** and position (**b**+**c**) or **b**. [e] Fluoroarene (1.0 equiv), **2** (3.0 equiv), DMF (2.4 mL) + DMSO (5%). [f] $Pd(OAc)_2$ (15 mol %). [g] Purified by reversed-phase preparative HPLC; number in parentheses is the ratio of *E*/*Z*. [h] Fluoroarene (1.0 equiv), **2** (3.0 equiv), DMF (2.4 mL), PivOH (1.2 equiv). [i] $Pd(OAc)_2$ (20 mol %), PivOH (3.0 equiv).

It was also possible to further derivatize the perfluoroarylated alkenes through C−H functionalization. As depicted in Scheme 1, compound **5ba** reacted with **2f** or **2 m**, respectively, to form unsymmetrical bis-alkenylated products **7** in good yields. This strategy thus allows the selective installation of substituents at different positions and provides access to highly functionalized perfluoroarenes by catalytic methods. A 2-g-scale synthesis of **3a** was also performed in good yield (71%), indicating the good reliability of the process (see Supporting Information).

Scheme 1. Formation of Bis(alkenyl)perfluoroarenes



In conclusion, we developed an efficient, $Pd(OAc)_2$ catalyzed method for direct olefination of highly electron-deficient perfluoroarenes. The reaction scope includes both activated and nonactivated alkenes. Applications of alkenylated perfluoroarenes in design and synthesis of bioactive molecules are under active investigation in our laboratory.

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Supporting Information Available: Detailed experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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